REMARKS

As noted above, Applicants hereby request that the Amendment after Final Office Action filed with the Office on January 30, 2009 ***not*** be entered upon receipt of the present RCE. The status of the claims presented below reflects the January 30, 2009 amendment not being entered into the file. The claims status identifiers and amendments presented herein reflect amendments versus the claims presented in the amendment dated August 19, 2008.

Claims 27, 29-33, 35-39, 41-45 and 47-56 are pending in the present application. By virtue of this response, claims 28-29, 31, 34-35, 37, 40-41, 43, 46-47, 49, and 53-56 have been cancelled, claims 27, 30, 32-33, 36, 38, 39, 42, 44-45, 48, 50-51 have been amended and new claims 57-62 have been added. Accordingly, upon entry of this amendment, claims 27, 30, 32-33, 36, 38, 39, 42, 44-45, 48, 50-52 and 57-62 will be under consideration.

The specification is amended to correct minor typographical errors, where both the error, and its correction, would have been obvious to the skilled artisan at the time of filing the present application. Further, the amendments are also supported by Figure 6. No new matter is believed to have been added by way of these amendments.

Support for the new and amended claims can be found throughout the specification, including the claims, as originally filed and, in particular at page 5, lines 19-36, in Example 2 (particularly pages 17-18, bridging ¶, page 27, lines 14-34), Example 3 (particularly pages 29-30, bridging ¶and page 31, lines 15-37), and Figures 6-9. Additional support can be found in claim 3 of the PCT application (as numbered in the PCT publication of the International Publication of which this is the US National Phase of which the present case is the 371 national phase application). Applicants note that amendment of claims 30, 32, 36, 38, 42, 44, 48, and 50 updates the claim dependency for these claims taking into account claim cancellations.

Further, additional support for the polydispersity of 1.78 can be found in, for example, Figure 6. It is well known to the person skilled in the art that the following formula is used to determine polydispersity:

$K_{av} = V_e - V_o / V_t - V_o$.

After determining the modal K_{av}, the polydispersity is calculated by multiplying the modal K_{av} by 2, and this figure is then added to 1. As seen in Figure 6, the hyaluronan is eluted as a modal K_{av} of 0.39. The polydispersity of the 890,000 Da hyaluronan is therefore calculated at 1.78.

No new matter is believed to have been added by way of these amendments.

With respect to any claim amendments or cancellations, Applicants have not dedicated to the public or abandoned any unclaimed subject matter. Applications expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Regarding the Prior-Submitted Declaration of Dr. Tracey Brown

The Examiner states that the Declaration filed with Applicant's response of August 19, 2008 does not identify the rule under which it was filed. The Examiner kindly invites Applicants to correct the Declaration in this response.

In response, Applicants submit that the declaration should have been identified as a declaration under 37 CFR §1.132.

Regarding the Supplemental Information Disclosure Statement (SIDS)

Applicants thank the Examiner in advance for her review of the cited references and return of the initialed SB/08. Should copies of any of the references not be accessible to the Examiner, she is encouraged to contact the undersigned prior to the issuance of a further action and additional copies will be provided.

Response to Interview Summary and Request for Examiner Interview

Applicants thank the Examiner for her time and willingness to participate in the telephonic interview with Dr. Gladys Monroy (attorney for Applicants) and Dr. Kimberly Bolin (patent agent for applicants) on August 6, 2009.

Applicants have reviewed the Interview Summary (mail date August 17, 2009) and find the Examiner's indication of the interview participants and summary of the content of the telephonic interview to be accurate.

Applicants believe that this communication fulfills Applicants' duty to provide a response to the Interview Summary. Should the Examiner not agree, she is requested to contact the undersigned at her earliest convenience.

Applicants further thank the Examiner for her time and consideration of the amendments and remarks presented herein. Should the amendments and remarks presented herein not fully address the Examiner's concerns, the Examiner is urged to contact the undersigned regarding any outstanding issues prior to the issuance of a further action on the merits.

Rejection Under 35 U.S.C. § 102

A. Claims 27, 33, 39, and 45 stand rejected under 35 U.S.C. § 102(e) for allegedly being anticipated by or, in the alternative, under 35 U.SC. § 103(a) as allegedly obvious over Falk *et al.* (U.S. Patent No. 5,985,850).

While not acquiescing to the Examiner's remarks regarding the alleged anticipation or obviousness of the previously presented claims, Applicants assert that the presently amended claims are neither anticipated nor rendered obvious by Falk *et al.* Applicants present the amended claims in an effort to further prosecution of the present application.

As an initial matter, Applicants note that previously pending claims 28-32, 34-38, 40-44, 46, and 52-56 were not rejected over Falk *et al.* as either anticipated or obvious. Applicants further note that claims 27, 33, 39 and 45 (the pending independent claims) have been amended, in part, to incorporate the molecular weight limitations of dependent claims 29, 35, 41, and 51, respectively (claims 29, 35, 41, and 51 are therefore canceled by virtue of this amendment).

Applicants therefore believe that based on at least the Examiner's own reasoning as applied to previously pending claims 29, 35, 41, and 51, amended independent claims 27, 33, 39 and 45 (and therefore their dependent claims) are neither anticipated nor rendered obvious by Falk *et al.*

For the clarity of the record, Applicants also note that Falk *et al.* does not disclose the systemic administration of 890,000 Da modal molecular weight hyaluronan (hereafter "HA") and chemotherapeutic agents. While the examples of Falk *et al.* are silent as to the molecular weight of HA administered to patients with cancer, the preferred HA taught by Falk *et al.* is characterized as having a molecular weight range of 150,000-225,000 Da, which falls well below the modal molecular weight of 890,000 Da recited in the amended claims. *See e.g.,* col. 17, line 33 through col. 18, line 28. An alternative formulation of HA disclosed as "successfully employed" (without supporting data) by Falk *et al.* is the LifeCore™ Biomedical, Inc. HA, characterized by a molecular weight of "<750,000 Daltons." (*See* col. 18, lines 33-58).

The teaching of Falk *et al.* with regard to higher than 730, 000 Da molecular weight HA is made in connection with treatment of the eye (*see* col. 18, line 62 through col. 19, line 25, particularly "f" at lines 14-23) and references US Pat No. 4,141,973 ("Balazs *et al.*"; cited in the SIDS co-filed herewith). Balazs *et al.*, which is referenced by Falk *et al.,* teaches the use of HA of greater than 750,000 Da, preferably greater than 1,200,000 Da for ocular (*e.g.,* after intravitreal and other intraocular surgery), intraarticular uses (*e.g.,* supplementation of synovial fluid, after joint surgery, etc.) and topical applications as a barrier to water and microorganisms in skin wounds. *See e.g.,* col. 14, line 8 through col. 15, line 48.

Falk *et al.* does not teach the systemic use of HA with 890,000 modal molecular weight HA for the treatment of cancer nor preparation of pharmaceutical formulations of anticancer chemotherapeutic agents and HA formulated for systemic administration.

For at least the above reasons, Applicants assert that Falk *et al.* clearly does not anticipate independent claims 27, 33, 39 and 45 and therefore their dependent claims.

With regard to the alleged obviousness of independent claims 27, 33, 39 and 45, as noted above, these amended claims recite the molecular weight limitation of claims 29, 35, 41, and 51, which were not rejected by the Examiner as obvious over Falk *et al.* Further, there is no teaching or suggestion in Falk *et al.* that would lead the skilled artisan to predict the enhanced efficacy of chemotherapeutic agents when used in combination with HA of 890,000 and administered systemically. The disclosure of Falk *et al.* describes a wide variety of conditions (*see e.g.,* the table bridging columns 19-20) and chemicals and drugs (*see e.g.,* the table bridging columns 19-20), but without any teaching to the skilled artisan regarding the selection of combinations of HA of particular molecular weights for particular routes of administration or indications. The indications in the above-referenced table range from hair growth (indicated to be applied topically) and prevention of topical infections, to treatment of HIV and cancer, but, except for the reference to the Balazs *et al.* teachings described above, provides no teaching of what molecular weight HA is suitable for effective treatment of particular indications, other than teaching that HA of molecular weight 150,000-225,000 Da is the preferred HA disclosed, with HA of molecular weight less than 750,000 as a possible alternative.

There is nothing in Falk *et al.* to lead a skilled artisan to predict the enhanced efficacy of systemically administered HA of modal molecular weight 890,000 Da when combined with anticancer chemotherapeutics for the treatment of cancer, such as is demonstrated in the present application (*see e.g.,* Example 2 and Figure 7-9). Further evidence of the superiority of HA of molecular weights greater than even the alternative HA described by Falk *et al.* (which is less than 750,000 Da), is provided by the declaration of Dr. Tracey Brown under 37 CFT 1.132 and filed with the Office September 11, 2006 (*see e.g.,* Figure 1 (a &b) through Figure 3).

Thus, as noted previously, Applicants assert that the presently pending claims are neither anticipated by nor rendered obvious by Falk *et al.* and respectfully request withdrawal of the above rejections.

B. Claims 27, 33, 39, and 45 stand rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by della Valle *et al.* (U.S. Patent No. 5,422,053).

While not acquiescing to the Examiner's remarks regarding the alleged anticipation of the previously presented claims, Applicants assert that the presently amended claims are not anticipated by della Valle *et al.* Applicants present the amended claims in an effort to further prosecution of the present application.

As noted above with regard to Falk *et al.*, and as an initial matter, Applicants note that previously pending claims 28-32, 34-38, 40-44, 46, and 52-56 were not rejected over della Valle *et al.* as anticipated. Applicants further note that claims 27, 33, 39 and 45 (the pending independent claims) have been amended, in part, to incorporate the molecular weight limitations of dependent claims 29, 35, 41, and 51, respectively.

Applicants therefore believe that based on at least the Examiner's own reasoning as applied to previously pending claims 29, 35, 41, and 51, amended independent claims 27, 33, 39 and 45 (and therefore their dependent claims) are not anticipated by della Valle *et al.*

For the clarity of the record, Applicants also note that della Valle *et al.* does not disclose the systemic administration of 890,000 Da modal molecular weight hyaluronan (hereafter "HA") and chemotherapeutic agents (or systemic formulations of this combination of HA and chemotherapeutic agents), instead, della Valle discloses the use of HA of molecular weight 500,000 to 730,000 Da for use in intraocular and intraarticular injections and HA of molecular weight of 50,000 to 100,000 for use in wound healing (topical application, intradermal injection). *See* Abstract, col. 3, lines 12-24 and 48-64, *etc.*)

With regard to the della Valle *et al.,* disclosure of 5-flurouracil (5-FU) and methotrexate in col. 24, lines 60-61 as cited by the Examiner, Applicants note that these lines, when taken in context with the paragraph in which they appear teach that the HA and 5-FU/methotrexate are formulated for *dermatological* applications, not formulated for systemic (*e.g.,* intravenous) use. *See below:*

> *Examples of active substances to be used alone or in combination or together with other active principles in* ***dermatology*** are: therapeutic agents such as anti-infective, antibiotic, antimicrobial, anti-inflammatory, cytostatic, ***cytotoxic***, antiviral, anesthetic agents, and prophylactic agents, such as sun shields, deodorants, antiseptics and disinfectants. Of the antibiotics the following are of particular note: erythromycin, bacitracin, gentamicin, neomycin, aureomycin, gramicidin and their associations; of the antibacterials and disinfectants: nitrofurazone, mafenids, chlorhexidine, and derivatives of 8-hydroxyquinoline and possibly their salts; of the anti-inflammatory agents: above all the cortocosteroids such as prednisolone, dexamethasone, flumethasone, clobetasol, triamcinolone acetonide, betamethasone or their esters, such as valerianares, benzoates, dipropionates; ***of the cytotoxics: fluorouracil, methotrexate, podophyllin***; and of the anesthetics: dibucaine, lidocaine, and benzocaine. This list is of course only for illustrative purposes and any other agents known or described in literature may be used. Of the examples mentioned for *ophthalmology and dermatology*, it is possible to determine by analogy medicaments according to the present invention which are useful in the above mentioned fields of medicine, such as for example in otorhinolaryngology or odontology or in internal medicine, for example in endocrinology, where it is possible to effect treatments with preparations for intradermic absorption or absorption through the mucous, for example rectal or intranasal absorption, for example such as nasal sprays or inhalations in the oral cavity and in the pharynx. These preparations may, therefore, be for example anti-inflammatory, or vasoconstricting or vasopresors such as those already mentioned for ophthalmology, vitamins, antibiotics, such as those mentioned above, hormes, chemiotherapeutics, antibacterials, etc., these also as mentioned above for use in dermatology. (Col. 24, line 49 through col. 25, line 17. *emphasis added*).

Thus, for at least these reasons, the presently pending amended independent claims 27, 33, 39 and 45 (and therefore their dependent claims) are not anticipated by della Valle *et al.* and Applicants respectfully request withdrawal of the above rejection.

Rejection Under 35 U.S.C. § 103

Claims 27-56 stand rejected under 35 U.S.C. § 103(a) allegedly as being unpatentable over della Valle et al. (U.S. Patent No. 5,442,053) according to the rejections of record and modified to account for the amendment to claims 28, 34, 40, 46, and new claims 53-56.

While not acquiescing to the Examiner's remarks regarding the alleged obviousness of the previously presented claims, Applicants assert that the presently amended claims are not rendered obvious by della Valle *et al.* Applicants present the amended claims in an effort to further prosecution of the present application.

As noted above with respect to the rejection of claims 27, 33, 39 and 45 under 35 USC 102(b) over della Valle *et al.*, della Valle *et al.* does not teach the use of HA of greater than 730,000 Da molecular weight nor the systemic administration (*e.g.,* intravenous , *etc.*) of HA in combination with chemotherapeutic agents, (Neither are systemic formulations of HA of 890,000 Da modal molecular weight and anticancer chemotherapeutic agents taught.

Della Valle *et al.* describe the isolation and use of two different molecular weight fractions of HA. These fractions are HA of molecular weight 500,000 to 730,000 Da ("HYALSTINE") and HA of molecular weight of 50,000 to 100,000 Da ("HYALECTIN"). The lower molecular weight fraction (50,000 to 100,000 Da) is disclosed as being suitable for use topically in wound healing, while the higher molecular weight fraction (500,000 to 730,000 Da) was identified as suitable for use intraocularly in ocular surgery as a substitute for endobulbar liquids and intraarticularly in therapy in connection with traumatic and degenerative diseases of the joints. *See* col. 3, lines 48-64, *etc.* As quoted above with regard to the rejection under 37 CFR 102(b), additional dermatological formulations are also disclosed (*see e.g.,* cols. 24-25).

Della Valle *et al.,* do not teach systemic (*e.g.,* intravenous) use of either the 500,000 to 730,000 Da fraction or the 50,000 to 100,000 Da fraction of HA. Nor do della Valle *et al.* teach the combination of HA of modal molecular weight 890,000 Da with anticancer chemotherapeutic agents. Moreover, della Valle would not lead the skilled artisan to predict that systemic administration of HA of modal molecular weight 890,000 Da would enhance the efficacy of anticancer chemotherapeutics (or the usefulness of compositions formulated for such use) in the treatment of cancer. Thus, Applicants assert that della Valle *et al.,* does not render the pending claims obvious.

In addition, della Valle *et al.* actually teach that *different molecular weight fractions of HA have very different physical (e.g., viscosity) and biological properties.* Thus, these *different* molecular weight factions may (or may not) be useful for *different* indications and these *different* molecular weight factions may (or may not) be utilized by different routes of administration. *See e.g.,* col. 3, line 65 through col. 4, line 31, reproduced below (*emphasis added*).

> The first fraction isolated by the inventors has been named HYALASTINE, and has an average molecular weight of from about 50,000 to about 100,000. This HYALASTINE fraction has been determined to be suitable for therapeutic, veterinary and human use because of its wound healing activity. The second fraction isolated by the inventors has been labelled HYALECTIN, and has an average molecular weight of about 500,000 to about 730,000. This HYALECTIN fraction is suitable for use in ocular surgery as a substitute for endobulbar liquids and for veterinary and human therapy in traumatic and degenerative diseases of the joints.
>
> HYALASTINE can be administered either as an intradermal injection or it can be applied as a topical agent for wound healing. HYALECTIN, on the other hand, is suitable for intraocular and intraarticular injection.
>
> The present inventors have made *intensive studies on the various fractions of HA and, in a significantly more precise way than previously accomplished, have specifically determined the* ***therapeutically useful fractions of HA*** *and the inflammatory and* ***non-useful fractions of HA***. As a result of these studies, the present inventors have identified and investigated two specific characteristics of HA fractions, namely cell mobilization activity and intrinsic viscosity. The wound healing process in animals is facilitated by cellular mobilization, and particularly the mobilization of fibroblasts. On the other hand, cellular mobilization or proliferation activity (i.e., mytosis) is to be avoided in cases of surgery inside the ocular globe. This is particularly true in operations to correct retinal detachment where an increased rate of healing may cause harmful affects.
>
> The intrinsic viscosity is also an important parameter to be considered in determining the utility of a fraction of HA. A fraction having a *high intrinsic viscosity is useful for surgical uses*, in the therapy of diseases of the joints of a traumatic and degenerative nature, and for replacing endobulbar liquids. On the other hand, high viscosity is an *undesirable* characteristic for fractions to be utilized as drugs for facilitating wound healing. In fact, fractions to be utilized in wound healing should have low viscosity so as to be more easily used in practical application.
>
> The HYALASTINE fraction identified by the present inventors has been determined to have good mobilization or cell proliferation activity, and low viscosity characteristics. Accordingly, HYALASTINE has the characteristics *desirable* for a material useful in promoting wound healing. The same characteristics make the HYALASTINE fraction *undesirable* for use in intraocular or intraarticular-injection treatments.

There is no disclosure in della Valle that would allow the skilled artisan to predict the indications for which the particular HA of 890,000 Da modal molecular weight would be useful, nor any teaching or suggestion that would predict what route of administration would be suitable.

Thus, as noted previously, in addition to not disclosing or suggesting combinations of HA of 890,000 Da modal molecular weight and anticancer chemotherapeutic agents and their systemic administration in enhancing the efficacy of these agents in the treatment of cancer, della Valle *et al.* clearly does not lead the skilled artisan to predict the efficacy demonstrated by these formulations and methods, as evidenced by the disclosure of the present application and, in addition in the September 11, 2006 declaration of Dr. Tracey Brown (*see citations above*). Indeed, on considering the teaching of the reference as a whole, the skilled artisan at the priority date of the present application would not predict the surprising enhancement of anticancer chemotherapeutic agent efficacy when combined with 890,000 Da modal molecular weight HA administered systemically (*e.g.,* intravenously). Instead, della Valle *et al.* actually teach the skilled artisan the unpredictability of the biological effects of *different molecular weight ranges* of HA and the need to discover the uses and routes of administration for which he various molecular weight fractions are suitable.

Thus, for at least the reasons recited above, Applicants assert that the presently pending independent claims 27, 33, 39 and 45 (and therefore their independent claims) are not obvious in view of della Valle *et al.* In view of the above remarks and amendments, Applicants respectfully request withdrawal of the rejection of claims 27, 33, 39 and 45 (and their dependent claims.)

Applicants note that cancellation of claims 28-29, 31, 34-35, 37, 40-41, 43, 46, 49, and 53-56 renders the above-listed rejection moot with respect to these claims.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 229752005700. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: August 17, 2009

Respectfully submitted,

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